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# INVOLVEMENT OF METHYSERGIDE-SENSITIVE 5-HT RECEPTOR IN PUDENDAL NERVE INHIBITION OF NOCICEPTIVE AND NON-NOCICEPTIVE BLADDER ACTIVITY IN CATS

Hypothesis / aims of study
Understanding the neurotransmitter mechanisms involved in pudendal nerve inhibition of bladder activity could lead to identify new pharmacological targets for overactive bladder. Currently little is known about the effect of 5-hydroxytryptamine (5-HT) $_2$ receptor on micturition reflex. This study used methysergide, a non-specific 5-$HT_2$ receptor antagonist, and naloxone, an opioid receptor antagonist, to examine the involvement of these receptors in the inhibition of micturition reflex induced by pudendal nerve stimulation (PNS).

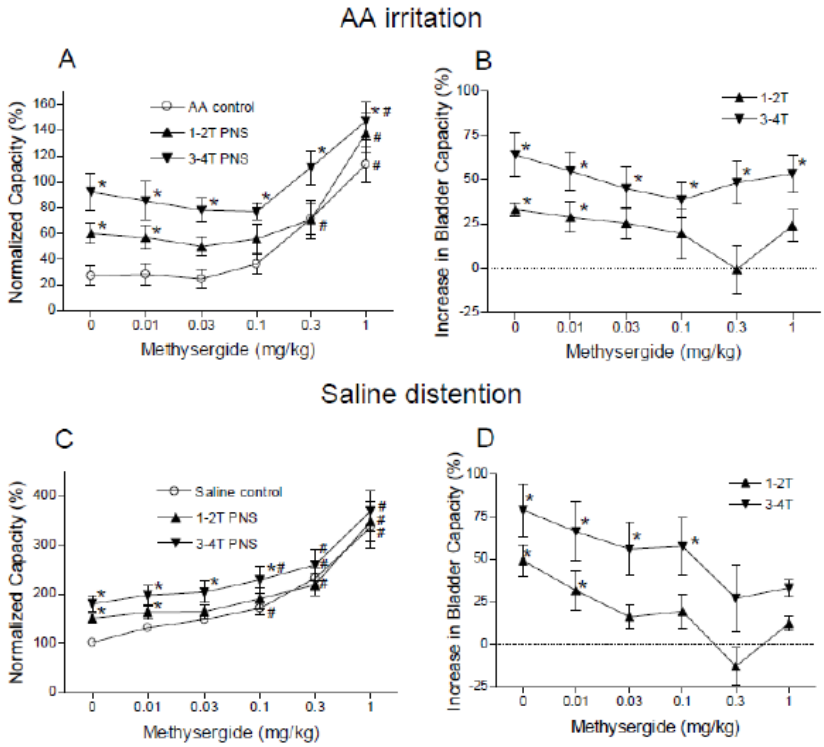
Study design, materials and methods
Experiments were conducted in 20 cats under α-chloralose anesthesia. A tripolar cuff electrode was applied around the right pudendal nerve and connected to a stimulator. Drugs were administered via the right cephalic vein. Pharmacological studies were performed in two experimental groups [i.e., acetic acid (AA) and saline group]. In both group, cumulative doses (0.01, 0.03, 0.1, 0.3, and 1 mg/kg) of methysergide and then naloxone (1 mg/kg) were given.

Results
AA irritated the bladder, induced bladder overactivity and significantly ($p < 0.0001$) reduced bladder capacity (BC) to 27.0 ± 7.4 % of saline control capacity. PNS (5 Hz, 0.2 ms) at 1-2 and 3-4 times the threshold (T) intensity for inducing an observable twitching of anal sphincter suppressed AA-induced bladder overactivity and significantly increased BC to 60.1 ± 8.0 % at 1-2T ($p < 0.0001$) and 92.2 ± 14.1 % at 3-4T ($p = 0.001$) of the saline control capacity. Methysergide (0.03-1 mg/kg, i.v.) suppressed PNS inhibition of bladder overactivity at low intensity (1-2T) but not at high intensity (3-4T) (Fig. 1A and B). During saline infusion PNS increased BC to 150.8 ± 9.9 % at 1-2T ($p < 0.01$) and 180.4 ± 16.6 % at 3-4T ($p < 0.01$) of the saline control capacity. Methysergide significantly increased BC at the doses of 0.1-1 mg/kg ($p < 0.05$) and suppressed pudendal inhibition (Fig. 1 C and D). After 1 mg/kg dose of methysergide, naloxone significantly ($p < 0.05$) reduced BC in AA condition, however, PNS-induced inhibition at 3-4T was still observed (Fig. 2A). On the other hand, naloxone did not change BC and PNS-induced inhibition in saline condition (Fig. 2B).

Interpretation of results
This study revealed that intravenous administration of methysergide significantly increased BC during both AA and saline infusion CMGs. It was also shown that methysergide completely eliminated the PNS-induced increase in BC during saline CMGs and partially eliminated this effect in AA irritated bladders, indicating a possible role of 5-$HT_2$ receptors in PNS inhibition. The descending 5-HT pathway from raphe nuclei in the brainstem has been known to inhibit nociceptive afferent input via activation of inhibitory interneurons in the spinal cord [1, 2]. Therefore, it is possible that the pudendal afferent firing might be transmitted to the brain and activate the raphe nuclei that drives the descending 5-HT pathway to activate 5-$HT_2$ excitatory receptors on inhibitory spinal interneurons that in turn suppress the micturition reflex. This possibility is supported by Radhakrishnan's report which indicates the involvement of spinal 5-$HT_{2A}$ receptors in the antinociceptive effect induced by transcutaneous electrical nerve stimulation [3]. In the previous studies, we showed in cats that intravenous naloxone excites the bladder and significantly reduces BC during saline infusion, but has no effect on the bladder during AA infusion, indicating that tonic enkephalinergic inhibition is only active during saline infusion. However, after methysergide administration the naloxone effect on bladder activity was reversed, i.e. the BC was reduced during AA infusion but not during saline infusion (Fig. 2). These results indicate that there is an interaction between 5-$HT_2$ and opioid receptor mechanisms in the micturition reflex pathway.

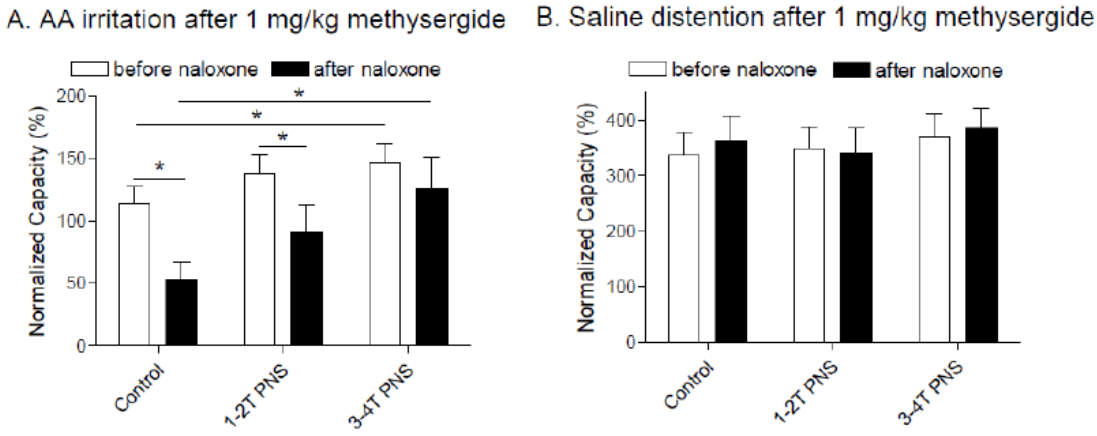
Concluding message
Based on these results, we conclude: (1) blockade of 5-$HT_2$ receptors increases the storage function of the bladder but does not alter the magnitude of the micturition reflex triggered by either nociceptive (AA irritation) or non-nociceptive (saline distension) stimulation of bladder afferents, (2) activation of 5-$HT_2$ receptors plays a partial role in PNS inhibition of nociceptive bladder overactivity and a major role in the inhibition of non-nociceptive bladder activity, (3) activation of opioid receptors is not important in PNS inhibition, but an interaction between opioid and 5-$HT_2$ receptor mechanisms does influence the regulation of bladder capacity.

Figure 1




* Indicates significantly ($p < 0.05$) different from AA control (A and B) or saline control (C and D). # indicates significantly ($p < 0.05$) different from BC measured before methysergide treatment (i.e. at 0 mg/kg of methysergide).

Figure 2




* Indicates a significant($p < 0.05$) differentce.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Disclosures

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